# Post transplant lymphoproliferative Disorders ( PTLD )

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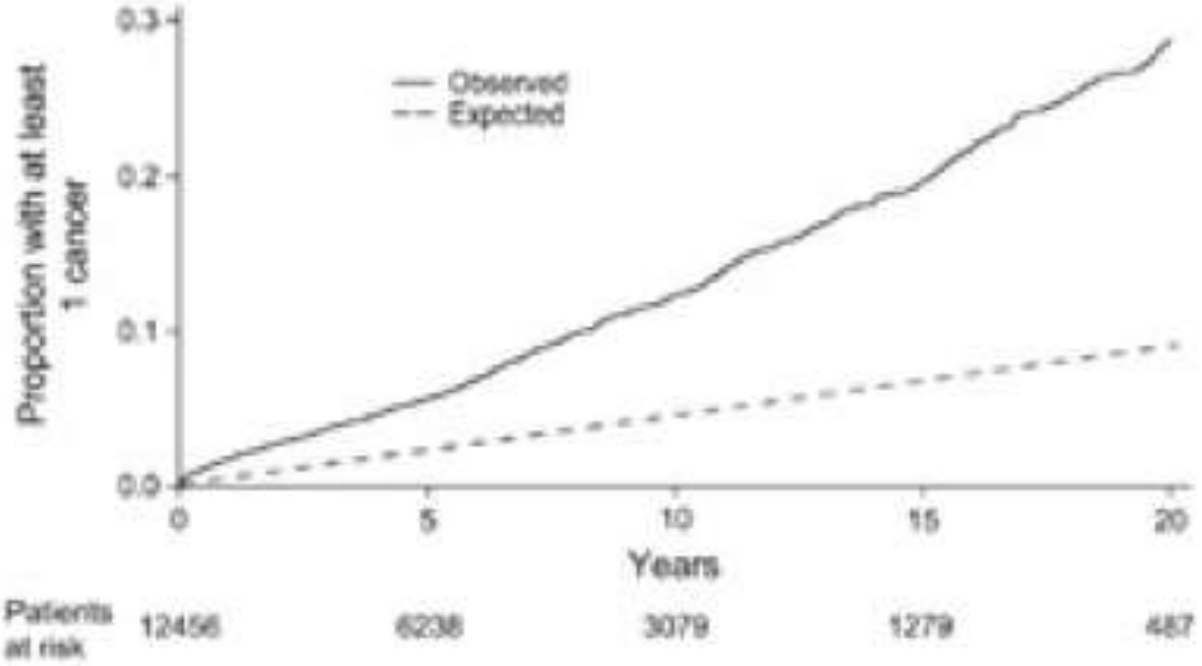
- The frequency of malignancy is increased in the post-transplant population,with a risk of ~ 2.5 – 3.0 x over an age-matched non-transplant population(as well as over age - matched dialysis patients).

- There is a huge variation between tumour types.
- Non-melanoma skin cancer (NMSC) has ~ 100 x greater risk ( ~ 200 x for squamous cell cancer); renal cell and urothelial cancer have ~ 10x risk, and breast cancer in ♀ has approximately equal risk.

- Cancer is recorded as the cause of death in ~ 10% of transplant recipients who die with a functioning graft (higher in some studies).

# Incidence of cancer after transplantation

ANZDATA: 13077 patients, 1980-2003




Cumulative risk of 1 cancer while allograft is functioning

Chapman et al. 2004

- Immune suppression is the most important risk factor, but others, including smoking, viral infections (e.g. EBV), and older age, are also relevant.
- There are rare reports of malignancy being transmitted from donor to recipient.

# Mechanisms

- Increased risk is more a function of overall immune suppressant burden than of a particular immune suppressive agent.

- Most immune suppressants impair the cell cycle and cell growth across many different cell types.

- Azathioprine interrupts the repair of UV light-associated DNA damage in the skin. This may be aided by the viral-induced inhibition of the p53 tumour suppressor gene.

- CNIs upregulate both TGF- B and VEGF, leading to increased angiogenesis and tumour spread in animal models.

- Sirolimus and other mTOR inhibitors reduce angiogenesis, so it is hoped they may be associated with less malignancy than other agents.

- Human herpes virus 8 (HHV-8) is associated with Kaposi's sarcoma.

- PTLD is associated with EBV proliferation.

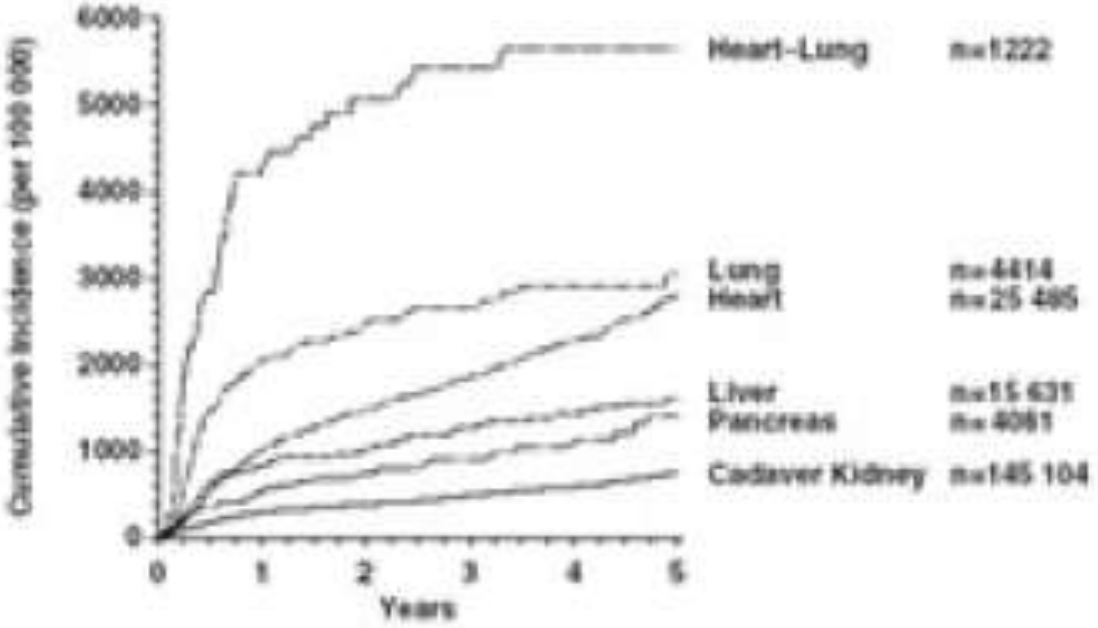
# Post-transplant lymphoproliferative disorders

- Second most common post-transplant malignancy after NMSC.
- PTLD encompasses a range of disorders, from an EBV-associated infectious mononucleosis syndrome early after transplantation through to non-EBV-(and often non-B cell-) associated malignant lymphoma, occurring late after transplantation.

**Table 5.15** WHO classification of PTLD

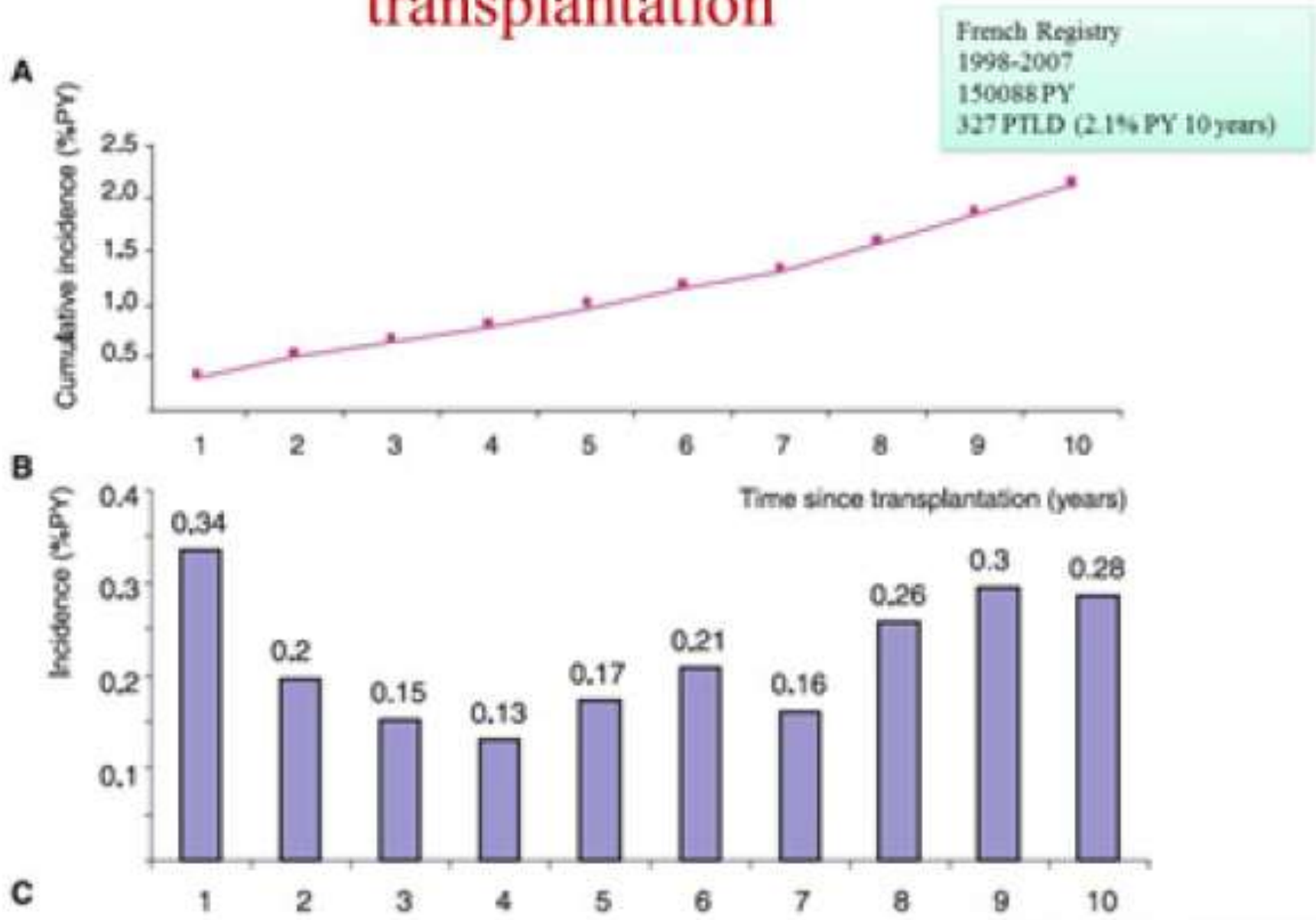
| Categories of PTLD | | | Comment |
|---|---|---|---|
| Early lesions | | Plasmacytic hyperplasia | Usually EBV +ve |
| | | Infectious mononucleosis-like lesion | Early |
| Polymorphic PTLD | | | Most common |
| | | | Usually EBV positive |
| Monomorphic PTLD | B cell neoplasms | Diffuse large B cell lymphoma | High-grade malignancy |
| | | Burkitt's lymphoma | Usually EBV –ve |
| | | Plasma cell myeloma | Late |
| | | Plasmacytoma-like lesion | |
| | T cell neoplasms | Peripheral T cell lymphoma | |
| | | Hepatosplenic T cell lymphoma | |
| | | Other rare types | |
| Classical Hodgkin's lymphoma-type PTLD | | | |

# Incidence of lymphoma after TX



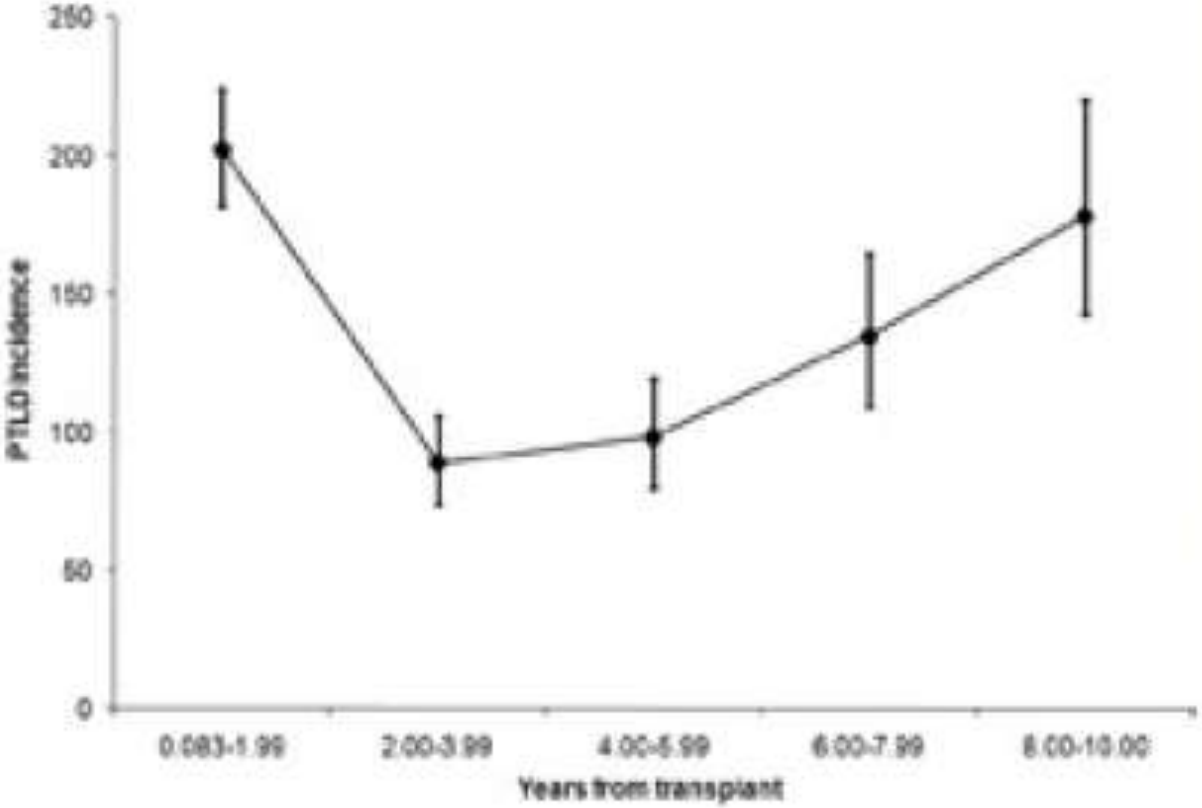

Opelz et al, AJT 2003 (CTS)

# PTLD cumulative incidence per year since transplantation




Caillard et al, AJT 2012

# Bimodal incidence of PTLD




**Early:**

- Associated to EBV+
- Graft
- Young

**Late:**

- Less associated to EBV
- Older
- Frequently extra-nodal

N= 156740

1999-2007

Quinlan et al, AJH 2011 (SRTR)

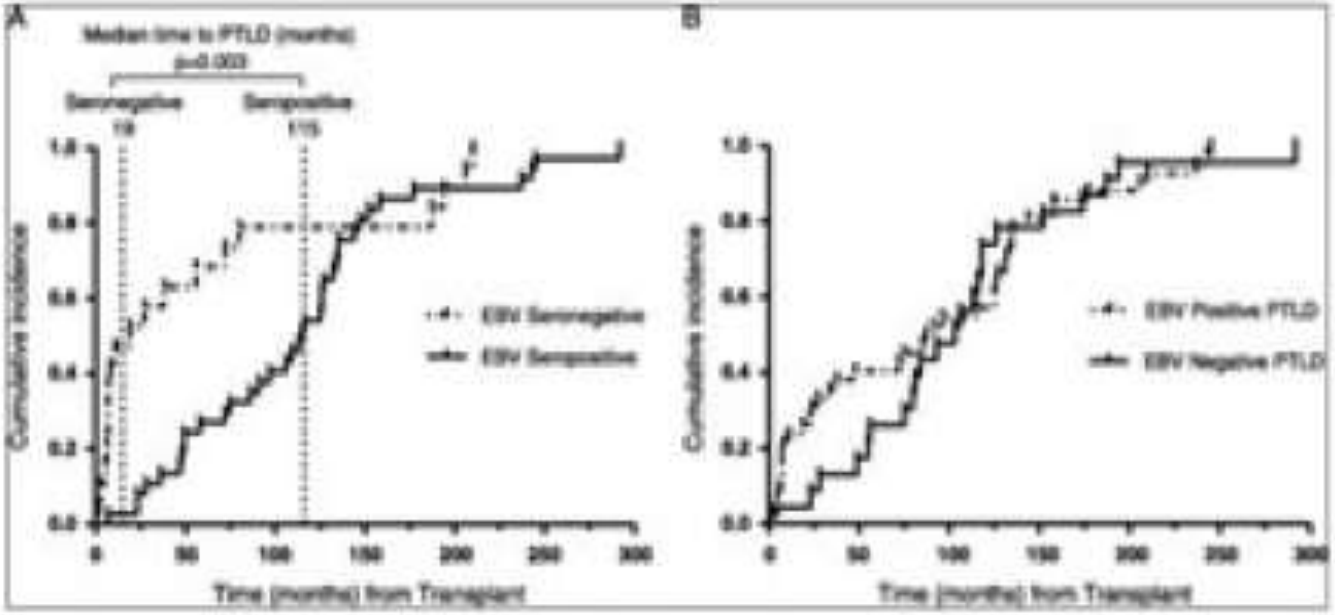
# EBV AND PTLD

- EBV is an overwhelming risk factor for PTLD.
- It has been known for nearly 40 years that EBV is linked to the development of Burkitts lymphoma and  to naso-pharengeal carcinomas.
- EBV is ubiquitous, with 95 % of the adult population in most centers having serological evidence of prior exposure.
- The possibility of reactivation is high if immunosupression is excessive.
- In children who undergo transplantation, approximately 50% are likely to be primary infection from the environment or directly from a virus positive graft or blood transfusion.

- EBV-associated malignancies affect approximately 1% of renal transplant recipients, the greatest incidence being in the first post-transplant year (0.2% / year) with reduced incidence thereafter (0.04 % per year).

- The wide spread lympho-proliferative response to EBV infection has histological features ranging from polymorphic B cell hyperplasia to monomorphic lymphoma. In some of these cases the lympho-proliferation results in tumor masses in which the lymphoid cells are usually of polycolonal type.
- In approximately one third of patients the lesions are monoclonal, the hallmark of true malignant lymphoma.
- Although the most common of malignant lymphomas that occur in transplant recipients are large cell lymphomas, the whole range of malignant lymphomas has been recorded, including lymphoblastic lymphomas, Hodgkins disease, and a variety of poorly defined malignancies

# Time from transplantation to PTLD diagnosis and EBV serostatus.




Morton et al. Transplantation 2013.

- Immune suppression disrupts CD8 +ve cytotoxic T cell EBV surveillance, allowing latently infected cells to undergo replication→eventual B cell transformation and immortalization.

- Recipient and donor EBV serological status should be known pre-transplant.

- EBV infection post-transplant: fever, malaise, pharyngitis,lymphadenopathy,hepatosplenomegaly, and lymphocytosis. Other non-PTLD manifestations include: hepatitis, pneumonitis, bone marrow suppression.

# PTLD RISK FACTORS

- EBV-seronegative recipient.
- Depleting antibodies and high levels of immune suppression.
- The development of a primary EBV infection.
- CMV infection
- For late PTLD: risk factors include older donor age and length of immune suppression

French Registry
1998-2007
150088 PY
327 PTLD (2.1% PY 10 ans)

**Table 5:** Multivariate analysis of risk factors for PTLD using a Cox proportional hazard model

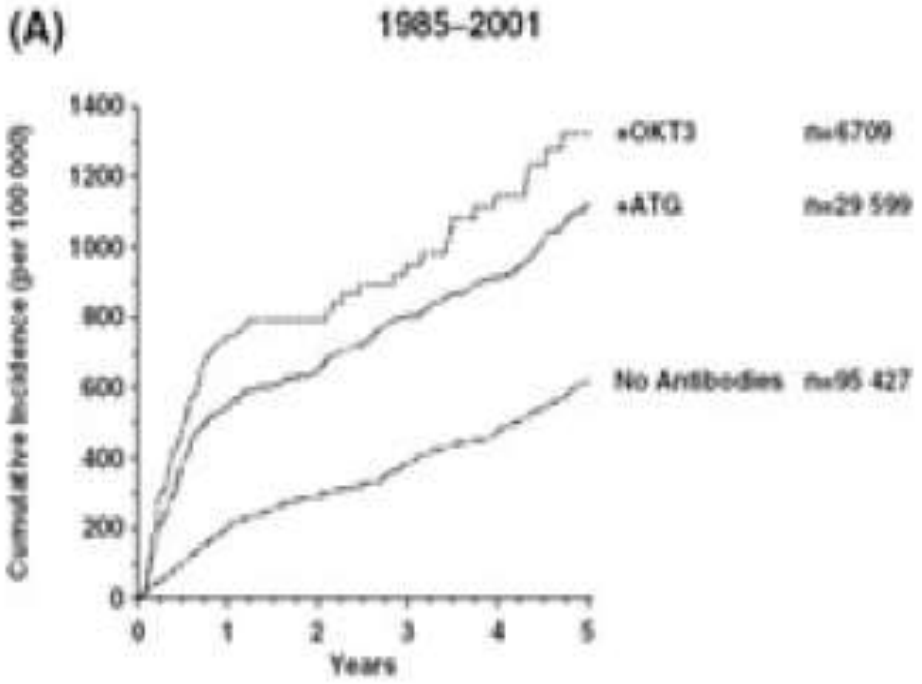
| Variables | Modalities | AHR | IC 95% | P |
|---|---|---|---|---|
| Recipient gender | Female | 1.05 | [0.76–1.46] | 0.76 |
| | Male | 1 | - | |
| Recipient age | 18–32 years | 1.06 | [0.60–1.87] | <0.0001 |
| | 33–46 years | 1 | - | |
| | 47–60 years | 1.87 | [1.22–2.86] | |
| | >60 years | 2.80 | [1.73–4.55] | |
| Period of transplant | 1998–1999 | 3.36 | [1.64–6.87] | 0.003 |
| | 2000–2001 | 3.08 | [1.55–6.15] | |
| | 2002–2003 | 1.90 | [0.93–3.91] | |
| | 2004–2005 | 1.64 | [0.79–3.40] | |
| | 2006–2007 | 1 | - | |
| SPK transplantation | No | 1 | - | 0.008 |
| | Yes | 2.52 | [1.27–5.01] | |
| EBV matching | All others | 1 | - | <0.0001 |
| | Donor + recipient− | 5.31 | [3.36–8.39] | |
| HLA matching | 0–4 mismatches | 1 | - | 0.008 |
| | 5 or 6 mismatches | 1.54 | [1.12–2.12] | |
| Induction therapy (polyclonal Ab or OKT3) | No | 1 | - | 0.05 |
| | Yes | 1.42 | [1.00–2.02] | |
| Cyclosporine | No | 1 | - | 0.17 |
| | Yes | 0.66 | [0.36–1.19] | |
| Tacrolimus | No | 1 | - | 0.19 |
| | Yes | 0.66 | [0.36–1.22] | |
| Azathioprin | No | 1 | - | 0.34 |
| | Yes | 1.30 | [0.76–2.19] | |
| MMF | No | 1 | - | 0.44 |
| | Yes | 1.22 | [0.74–2.02] | |

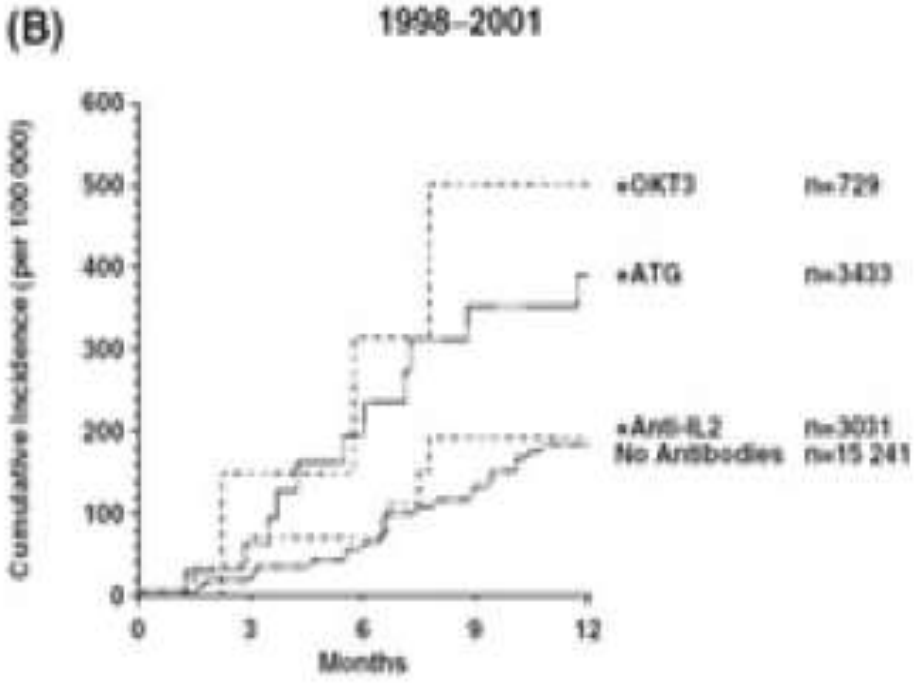
Caillard et al, AJT 2012

# Immunosuppresion and PTLDs

- PTLDs occur most commonly when intense immune suppression is used to treat resistant episodes of graft rejection.
- PTLDs regress completely in some patients when immunosuppressive therapy is reduced with or without concurrent antiviral therapy, sometimes with evolution to non-Hodgkins lymphoma or they progress to fatal outcome.
- It is now generally believed that PTLDs and malignant lymphomas are inevitable consequences of effective immunosuppressive therapy regardless of the particular immunosuppressive agents used.

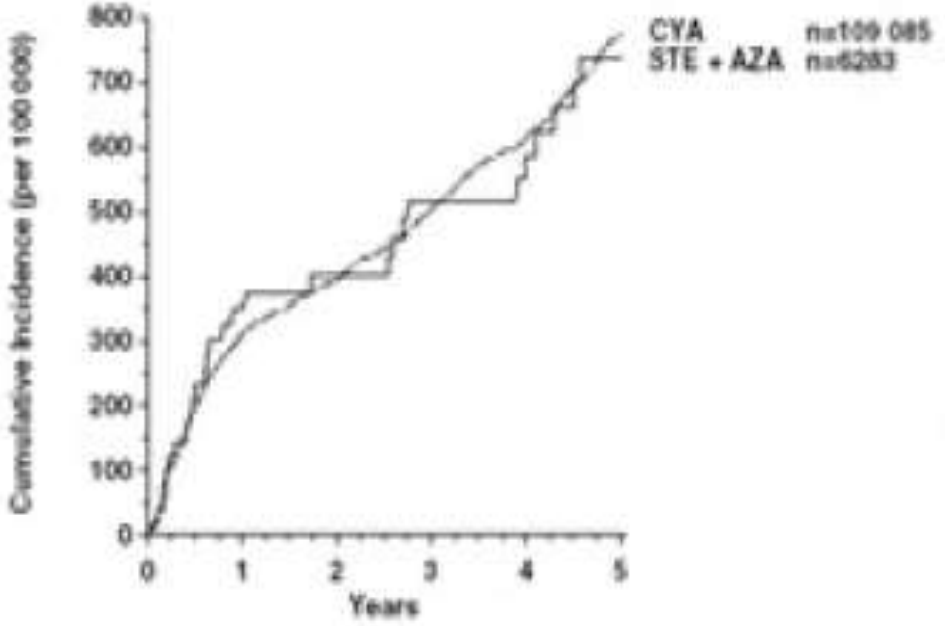
# PTLD and Immunosuppression




Opelz et al, AJT 2003 (CTS)

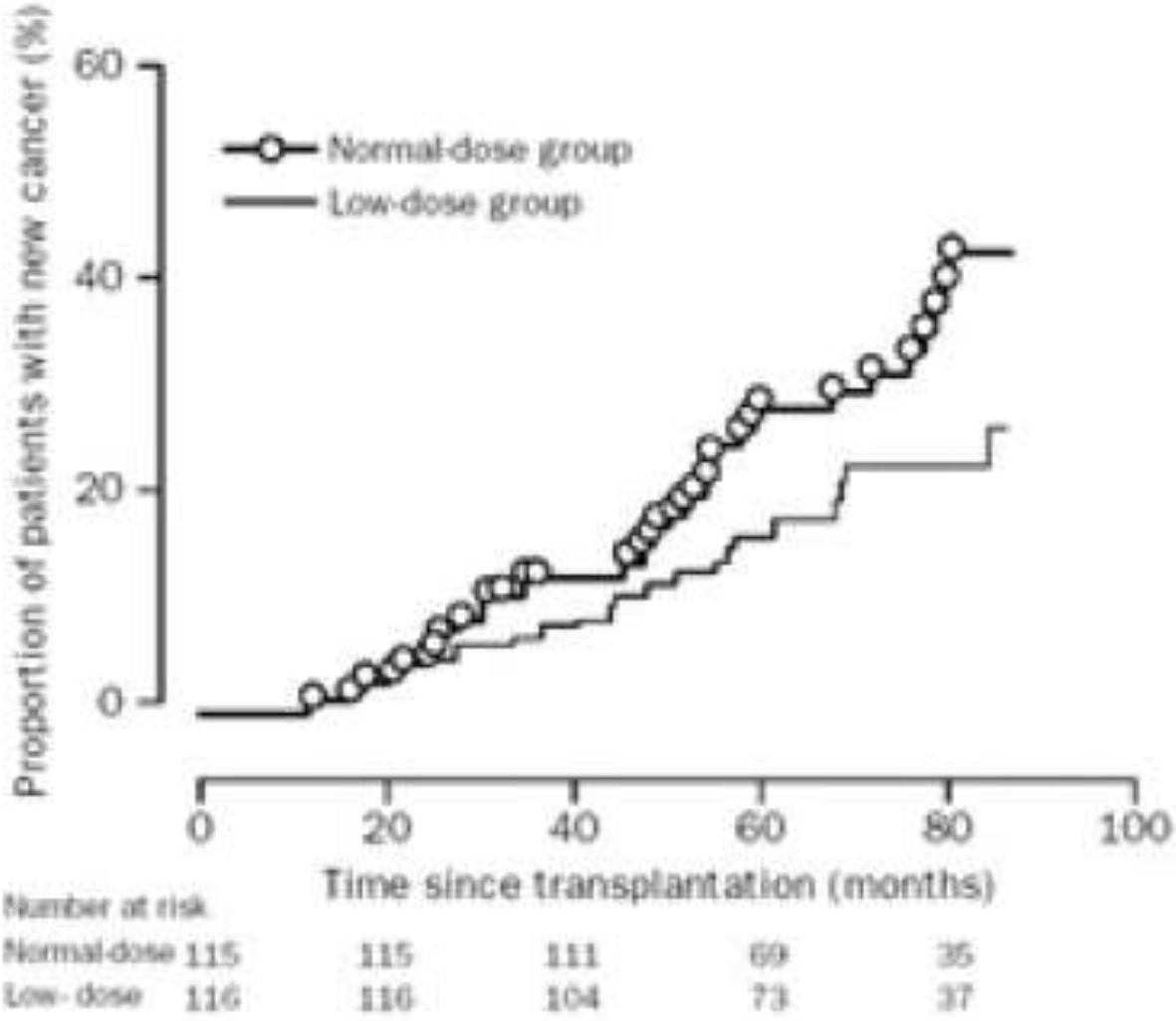
# PTLD and Immunosuppression





Opelz et al, AJT 2003 (CTS)

# CsA exposure and cancer




Dantal et al, Lancet 1998

# MMF

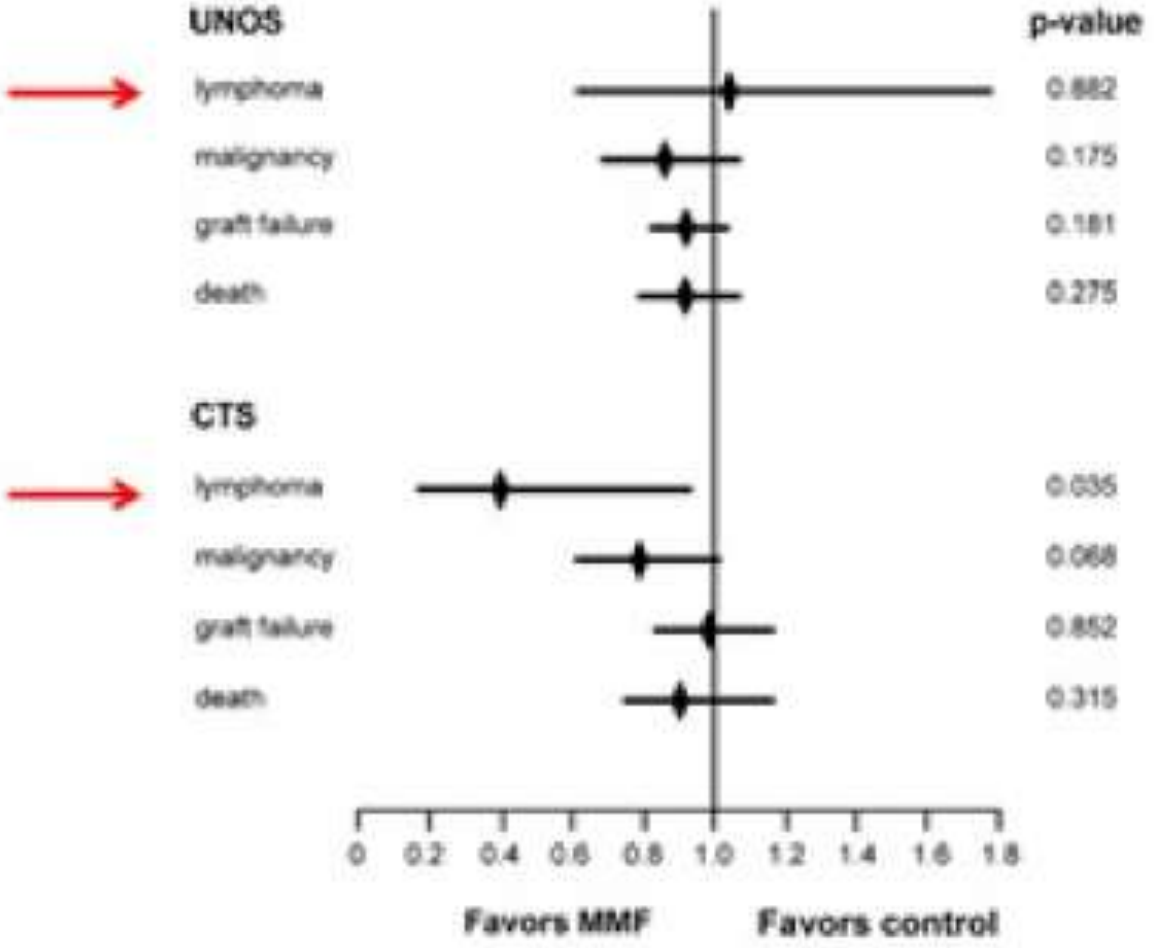
**Table 2:** Incidence of lymphoma, any malignancy, graft failure or death in mycophenolate mofetil versus nonmycophenolate mofetil cohorts (per protocol population)

| | OPTN/UNOS | | | CTS | | |
|---|---|---|---|---|---|---|
| | MMF (n = 4118) | Non-MMF (n = 4119) | p (chi-square) | MMF (n = 2628) | Non-MMF (n = 2629) | P (chi-square) |
| Lymphoma, n (%) | 27 (0.7%) | 27 (0.7%) | 0.999 | 7 (0.3%) | 24 (0.9%) | 0.002 |
| Malignancy, n (%) | 146 (3.6%) | 176 (4.3%) | 0.068 | 104 (4.0%) | 146 (5.6%) | 0.006 |
| Graft failure, n (%) | 538 (13.1%) | 544 (13.2%) | 0.848 | 291 (11.1%) | 302 (11.5%) | 0.631 |
| Deaths, n (%) | 302 (7.3%) | 316 (7.7%) | 0.560 | 201 (7.7%) | 239 (9.1%) | 0.058 |
| Any event, n (%) | 882 (22.4%) | 906 (22.0%) | 0.490 | 519 (19.8%) | 591 (24.5%) | 0.015 |

MMF does not seem to increase the risk of lymphoma and other types of neoplasia

Robson et al, AJT 2005

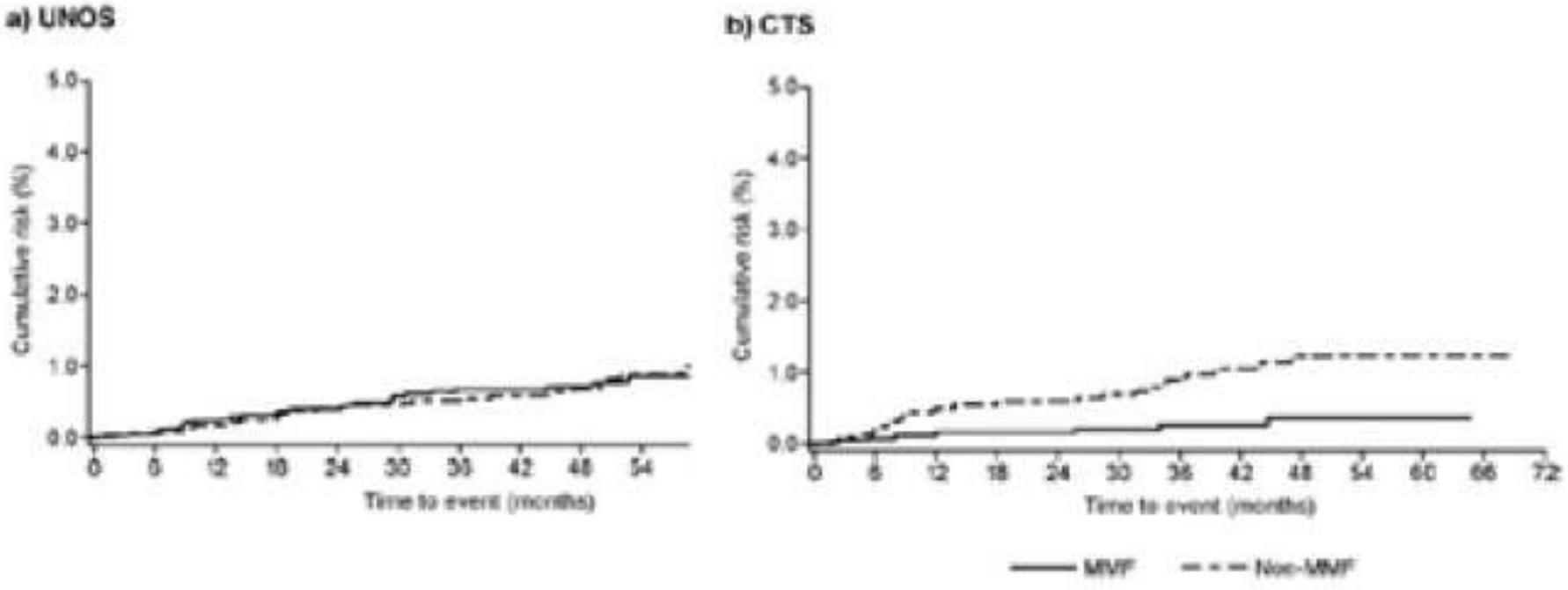
# MMF




- No higher risk of lymphoma
- A trend for lower incidence of malignancy

Robson et al, AJT 2005

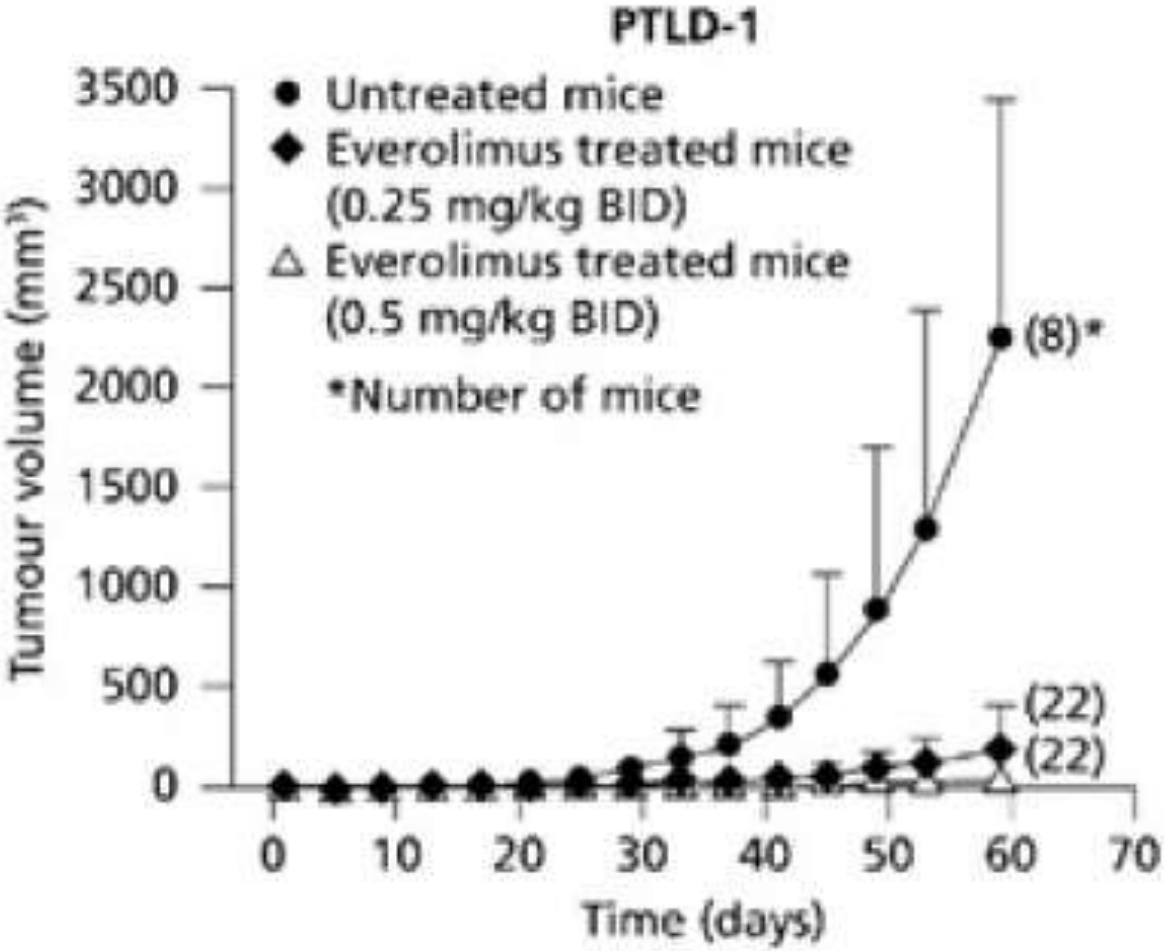
# MMF and lymphoma




Robson et al, AJT 2005

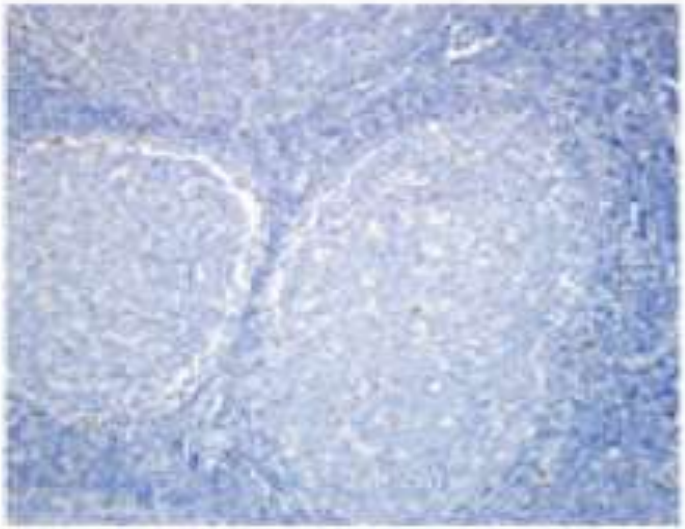
# PTLD and mTOR inhibitors

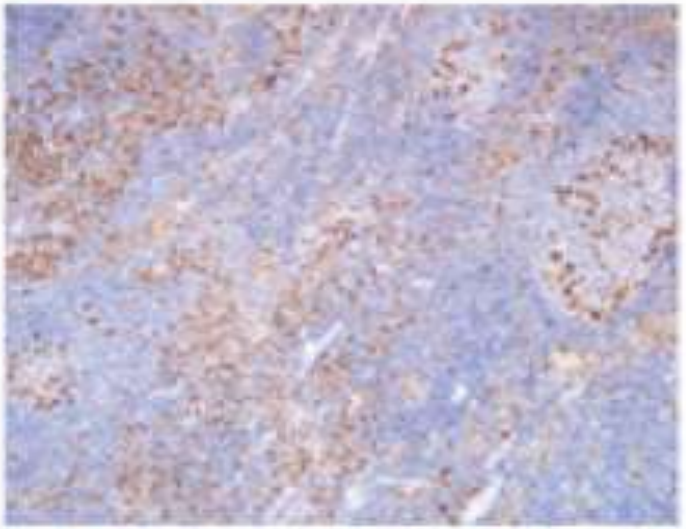
Effect of low-dose everolimus on *in vivo* growth of PTLD derived cells



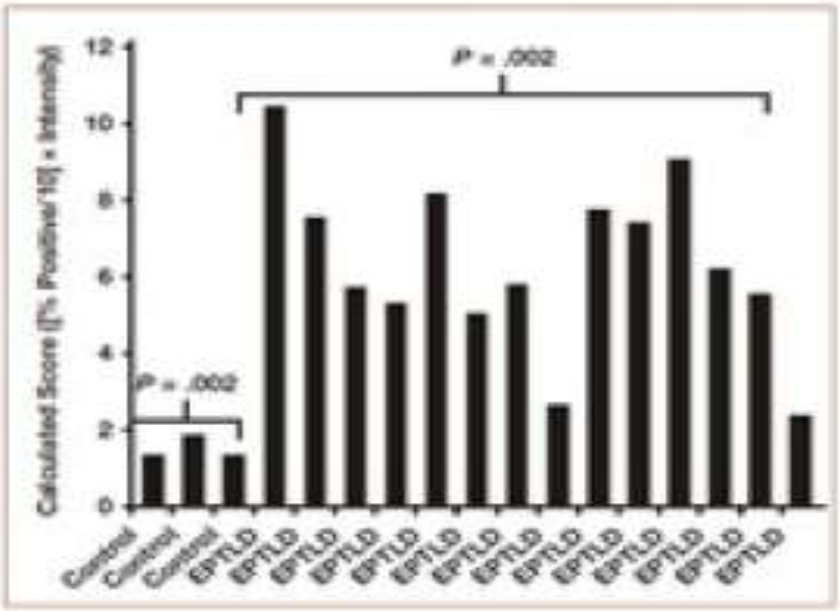

Majewski M et al, Transplantation 2003

# PTLD and mTOR pathway (in vivo)



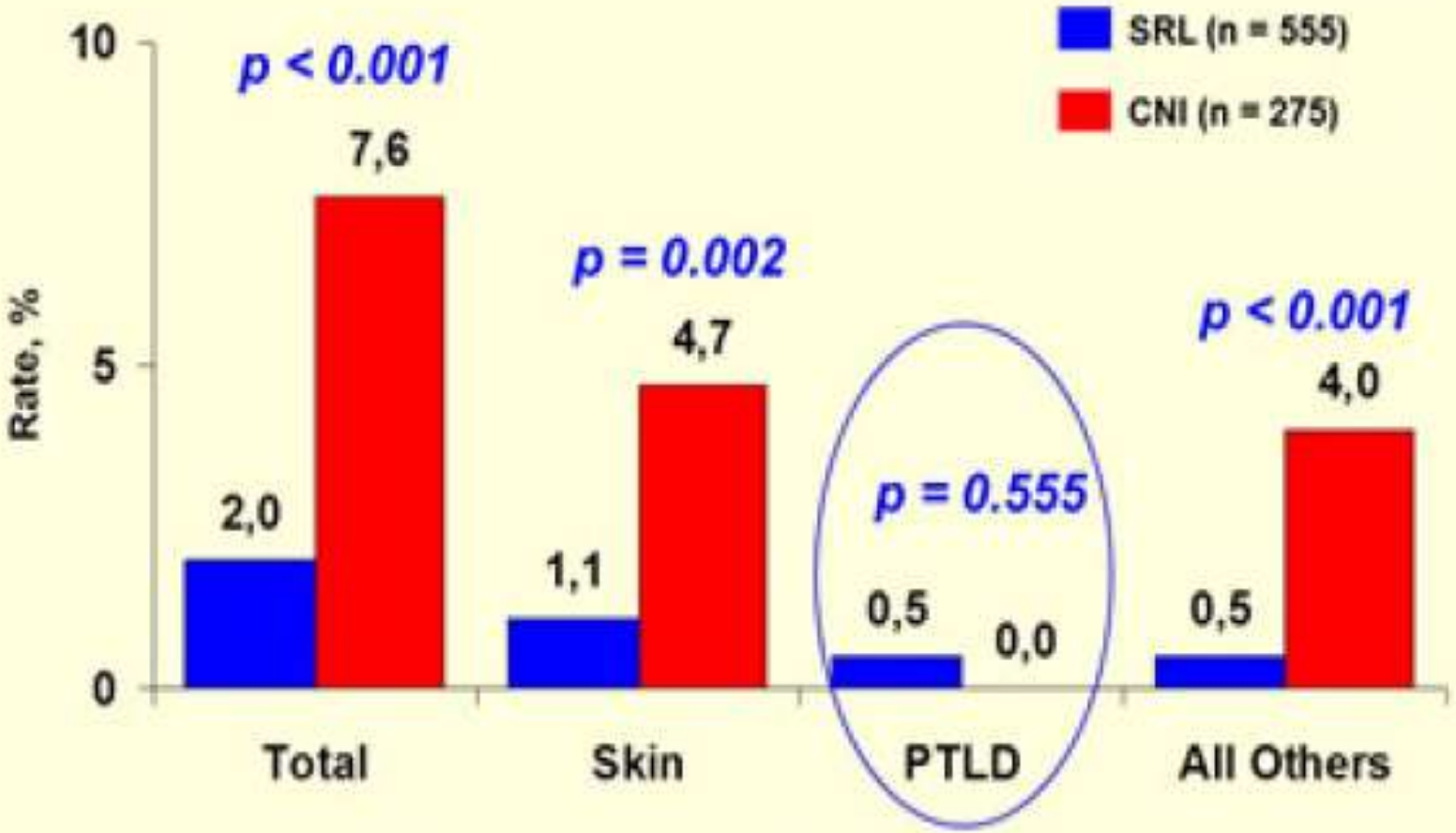


pS6



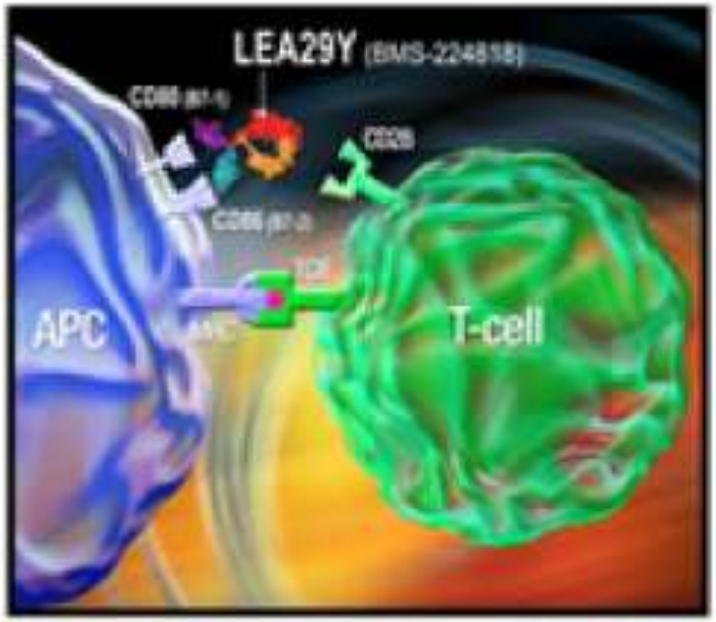

Nelson B et al. Hematopathology 2013

# Significantly Lower Malignancy Rates With SRL (Week 76)




Includes all randomized patients

# Belatacept: Selective Co-stimulatory Blocker




**Compared with CTLA4Ig, belatacept has:**

- 4-fold higher avidity for CD86
- 2-fold higher avidity for CD80
- ~10-fold more potent inhibition of T-cell activation *in-vitro*
- Increased efficacy at preventing rejection in primate renal transplant

Phase II[1]

- IM103100
- Proof of concept study (N=218)

Phase II Long-Term Extension[2]

- IM103100 - LTE
- Five-year safety and efficacy (N=94)

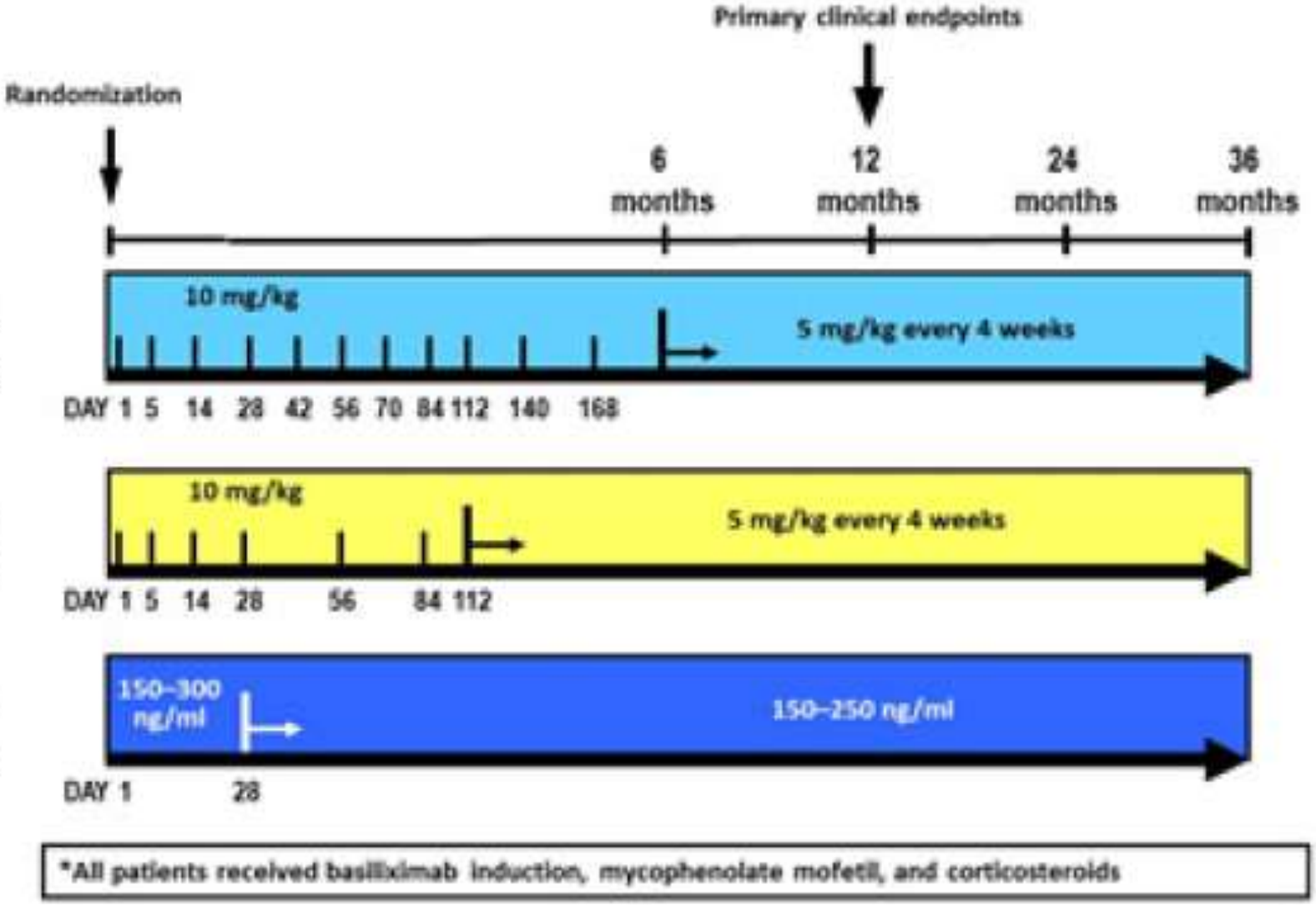
Phase III

- IM103008 - BENEFIT[3]
- Adult recipients of grafts from living and standard criteria deceased donors (N=666)

- IM103027 - BENEFIT-EXT
- Adult recipients of grafts from ECD kidney donors (N=543)

[1]Vincenti F et al. *N Engl J Med* 2005. [2]Vincenti F et al. *J Am Soc Nephrol* 2010 (epub ahead of print).
[3]Vincenti F et al. *Am J Transplant* 2010;10:535–46. [4]Durrbach A et al. *Am J Transplant* 2010;10:547–57.

# BENEFIT [Living and Standard Criteria Deceased Donors] and BENEFIT-EXT [Extended Criteria Donors] Phase 3 Clinical Trials of Belatacept in Kidney Transplantation



# PTLD: Pooled Analysis of Phase II and III Kidney Trials

| n (%) | Belatacept MI n=477 | Belatacept LI n=472 | CsA n=476 |
|---|---|---|---|
| Overall Malignancy | 46 (10%) | 27 (6%) | 34 (7%) |
| PTLD | 8 (2%) | 6 (1%) | 2 (<1%) |
| CNS PTLD | 6 (1.3%) | 3 (0.6%) | 0 |

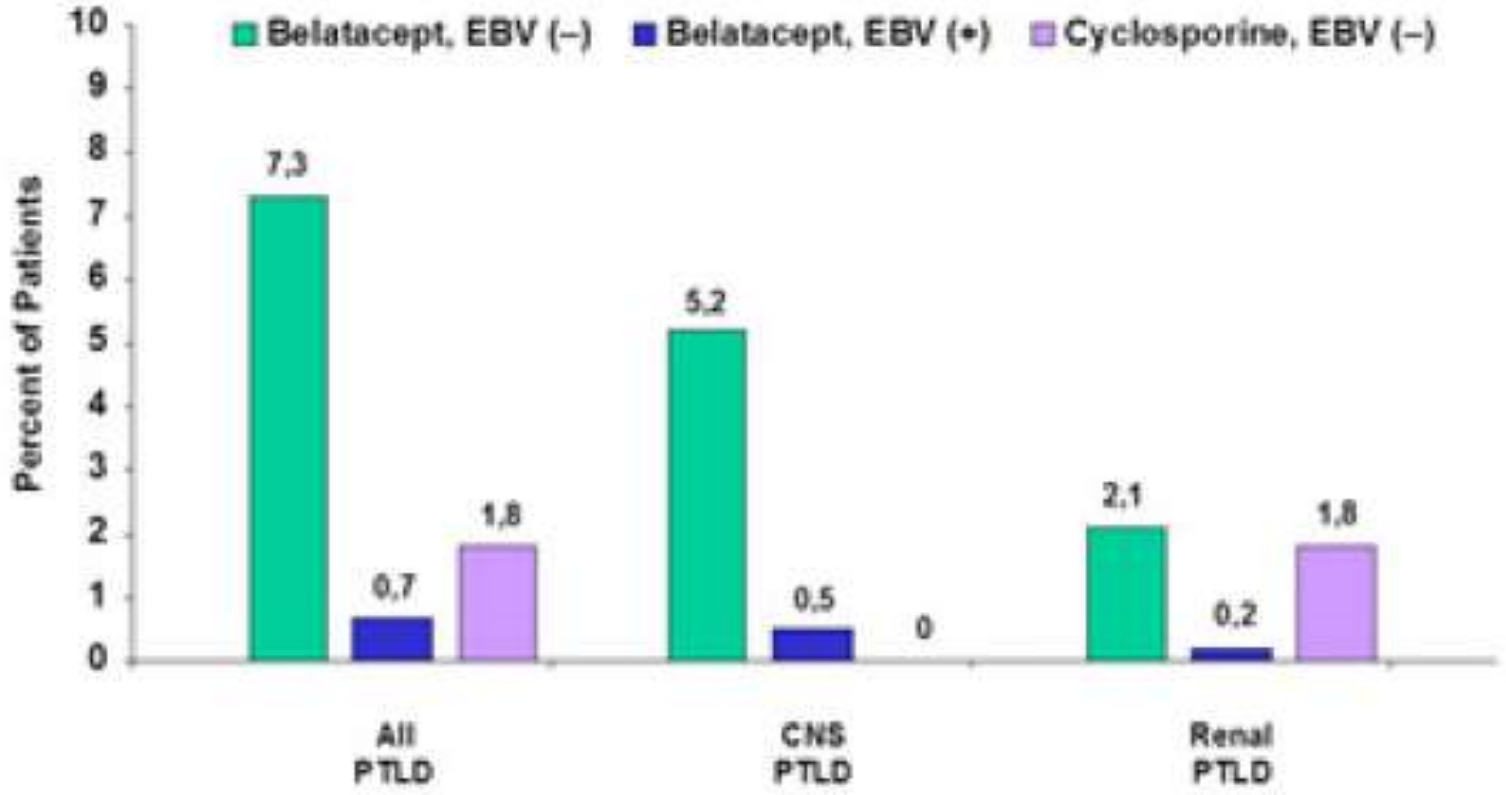
- Principal safety concerns with belatacept are CNS PTLD and PML
- Greatest risk of PTLD observed in EBV (-) patients and in patients receiving the belatacept MI regimen

Grinyó et al. Transplantation 2010; 90:1321-7.

# Increased Risk of CNS PTLD with Belatacept

| | Belatacept MI n = 477 | Belatacept LI n = 472 | Cyclosporine n = 476 |
|---|---|---|---|
| PTLD | 8 | 6* | 2 |
| Renal | 2 | 3 | 2 |
| Fatal | 1 | 1 | 2 |
| CNS | 6 | 3 | 0 |
| Fatal | 3 | 3 | 0 |

# EBV(–) Recipient Serostatus
# Strongest Risk Factor for PTLD (pooled data)




*Does not include 1 EBV unknown patient in the belatacept MI group, and 1 EBV unknown in the cyclosporine group. There are no cases of PTLD in CsA EBV(+) patients.

Grinyó et al. Transplantation 2010; 90:1521-7.

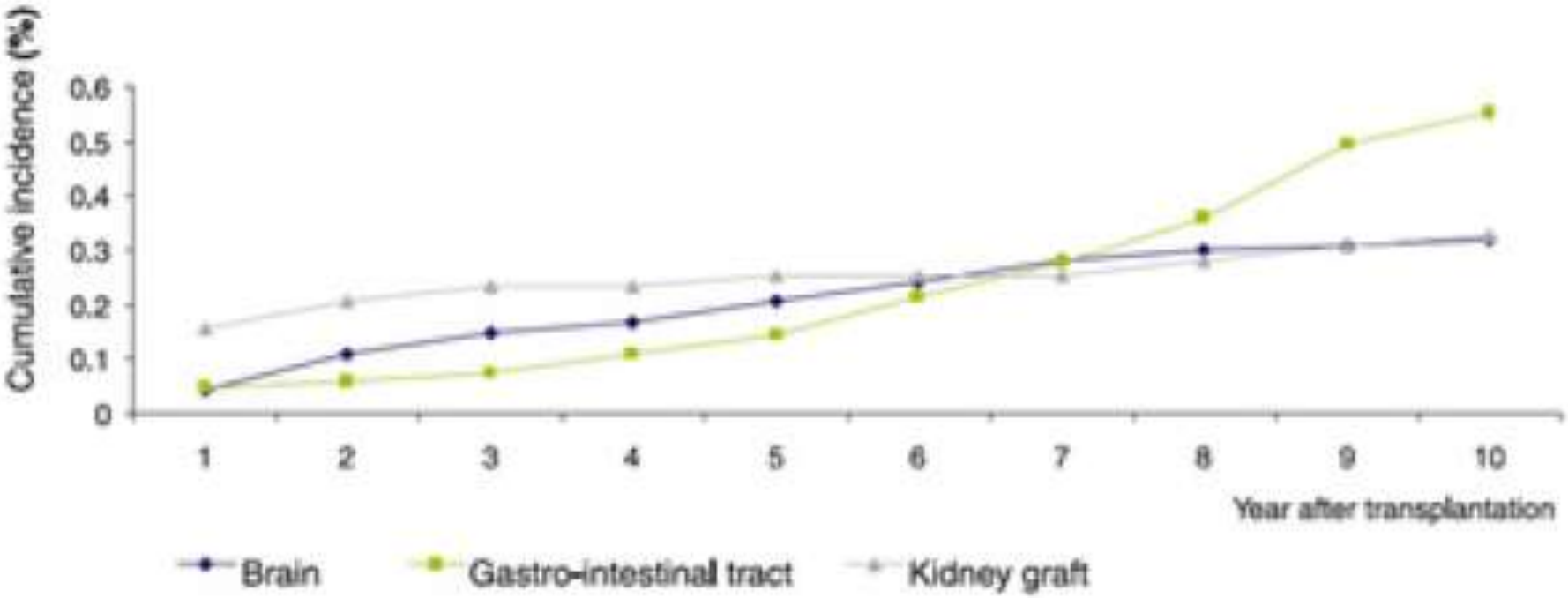
# PTLD with new immunosuppresants

- Early PTLD
- More frequent CNS location
- High lethality
- Strongly associated with EBV D/R serostatus: EBV primo-infection)
- Concomitant risk factors: CMV infection?

# Clinical presentation of PTLD

- May be asymptomatic. Weight loss, fever, night sweats, sore throat,malaise, anorexia, GI symptoms, and headache.
- Signs include: lymphadenopathy, hepatosplenomegaly, tonsillar enlargement, and focal neurological signs.
- Disease may be nodal or extranodal, localized (more common) or disseminated.
  Localized disease may occur in the transplant kidney.

# Ten-year cumulative incidence of PTLD as a function of the location of PTLD: graft, cerebral and digestive lymphomas




Caillard et al, AJT 2012

# Investigations

- Anaemia,↑serum urate,↑LDH.
- High-risk individuals (children and seronegative adults) should undergo surveillance, using EBV-DNA PCR.
- If suspected, whole body CT is usually undertaken (or CT-PET).
- Histopathology to confi rm diagnosis, and classify according to international criteria.
- Additional tests may include bone marrow examination and LP for CSF examination

# Prevention

- Attenuate cumulative immunosuppression
- Matching EBV serostatus (avoid D+/R-)
- EBV viral load monitoring in high risk population (mainly pediatric population)
- *Prophylactic infusion of EBV-specific CTL - HLA Matched in high risk population (mainly HSCT)*

# Management

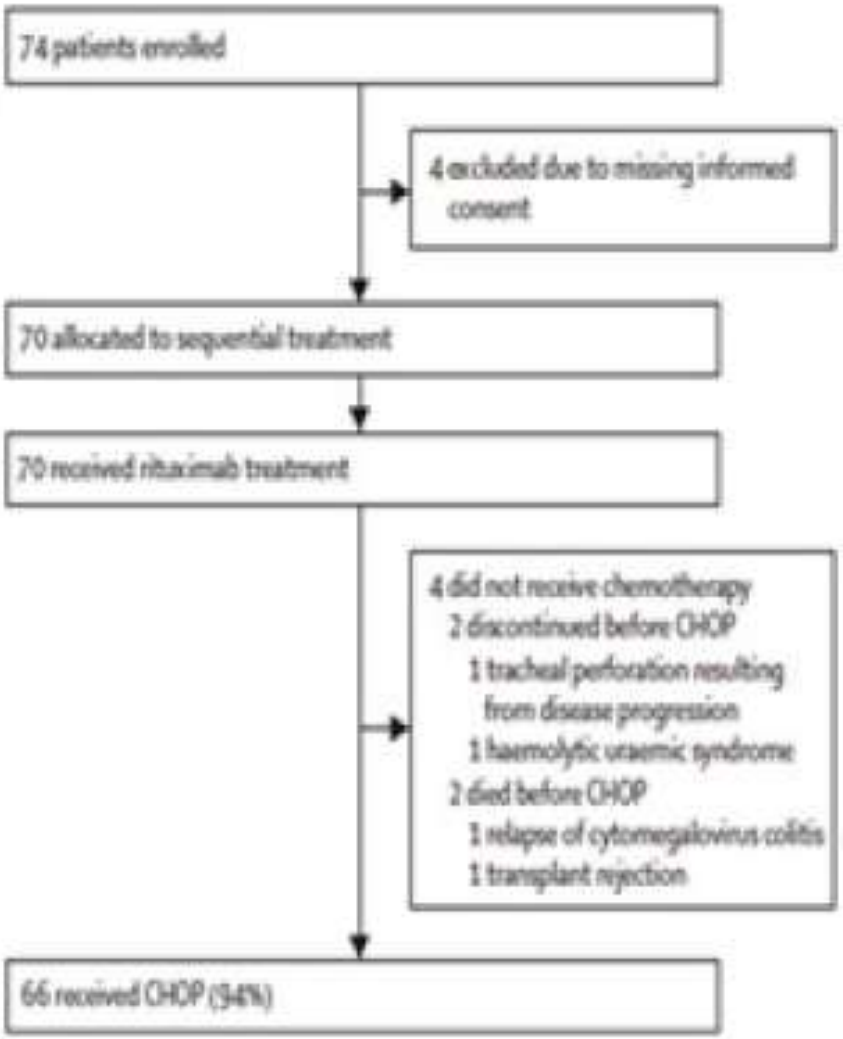
- A multidisciplinary approach, involving transplant physicians,histopathologists, and haemato-oncologists is essential.
- Histological type is crucial to planning therapy.

# Treatment of PTLD

① Reduction of immunosuppression
② Rituximab (anti-CD20)
③ Chemotherapeutic Agents
④ Adoptive immunotherapy

⑤ Risk of allograft rejection
⑥ Only for CD-20 + PTLD/Not for CNS PTLD
⑦ Treatment related mortality (mainly infection)
⑧ Difficult to obtain/poor evidence in SOT-PTLD

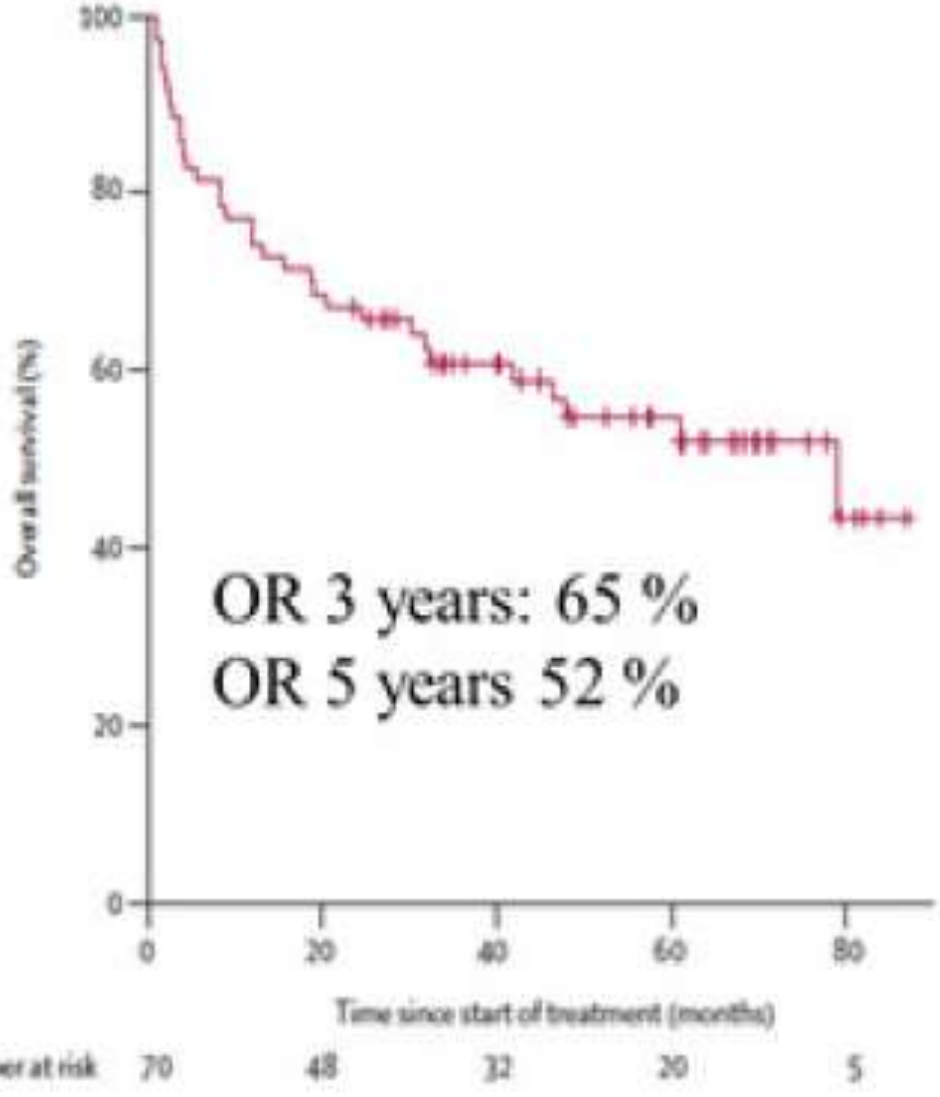
# RTX – CHOP Sequential therapy for PTLD

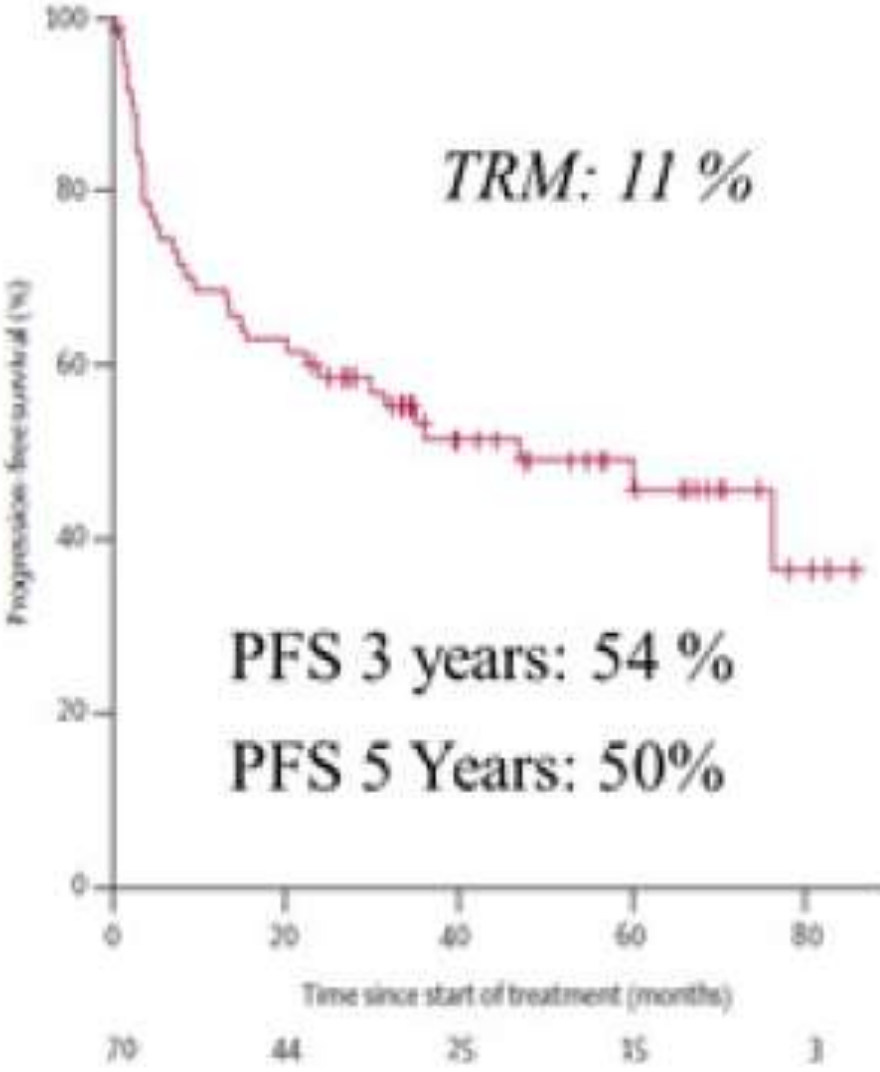



| | EBV-associated (n=29) | Non-EBV-associated (n=37) | p value |
|---|---|---|---|
| Age (years) | | | |
| Median (95% CI) | 43·5 (36·8–49·3) | 55·3 (48·6–57·7) | 0·0082 |
| Sex | | | |
| Male | 19/29 (66%) | 24/37 (65%) | 0·96 |
| Transplant type | | | 0·44 |
| Kidney | 10/29 (34%) | 18/37 (49%) | |
| Liver | 5/29 (17%) | 9/37 (24%) | |
| Heart | 7/29 (24%) | 7/37 (19%) | |
| Lung | 2/29 (7%) | 1/37 (3%) | |
| Heart and lung | 2/29 (7%) | 0/37 | |
| Kidney and pancreas | 2/29 (7%) | 2/37 (5%) | |
| Bone marrow | 1/29 (3%) | 0/37 | |
| Time from transplantation to PTLD (years) | | | |
| Median (95% CI) | 0·69 (0·38–4·14) | 9·30 (7·89–11·41) | <0·0001 |
| <1 year | 15/29 (52%) | 2/37 (5%) | <0·0001 |
| <2 years | 20/29 (69%) | 2/37 (5%) | <0·0001 |
| Histology | | | 0·39 |
| Polymorphic | 1/29 (3%) | 2/37 (5%) | |
| Monomorphic | 28/29 (97%) | 35/37 (95%) | |
| Burkitt's | 0/29 | 2/37 (5%) | |
| DLBCL | 26/29 (90%) | 27/37 (73%) | |
| Plasmacytoma-like | 1/29 (3%) | 1/37 (3%) | |
| Other B-cell | 1/29 (3%) | 5/37 (14%) | |

Trappe R et al. Lancet Oncology 2012

# RTX – CHOP Sequential therapy for PTLD



# Prospective therapy trials in PTLD

| | Patients | n | Transplant type | EBV association | Treatment line | Upfront therapy | Treatment | ORR (95% CI) | Median follow-up (months) | Median OS (months; 95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| Trappe | Adults | 70 | Kidney: 29/70 (41%)<br>Liver: 16/70 (23%)<br>Heart: 14/70 (20%)<br>Lung, heart+lung: 6/70 (9%)<br>Kidney+pancreas: 4/70 (6%)<br>Bone marrow*: 1/70 (1%) | 29/66 (44%) | First-line | R | This trial | 53/59: 90% (79-96) | 61 | 79·00 (33·6-124·8) |
| All rituximab monotherapy first-line trials combined[Trappe] | Adults | 98 | Kidney: 44/98 (45%)<br>Liver: 24/98 (24%)<br>Heart: 18/98 (18%)<br>Lung, heart+lung: 12/98 (12%) | 45/69 (65%) | First-line | R | All rituximab monotherapy first-line trials combined | 54/98: 55% (45-65) | 12–28 (range of follow-up) | 14·90–42·00 (range of median OS) |
| Choquet et al* | Adults | 43 | Kidney: 18/43 (42%)<br>Liver: 7/43 (16%)<br>Heart: 11/43 (26%)<br>Lung, heart+lung: 7/43 (16%) | 21/32 (66%) | First-line | R | 4 courses of rituximab monotherapy | 19/43: 44% (30-59) | 12 | 14·90 |
| Gonzalez-Barca et al* | Adults | 38 | Kidney: 22/38 (58%)<br>Liver: 13/38 (34%)<br>Heart: 2/38 (5%)<br>Lung, heart+lung: 1/38 (3%) | 14/20 (70%) | First-line | R | 4–8 courses of rituximab monotherapy | 25/38: 66% (50-79) | 28 | 42·00 |
| Oertel et al* | Adults | 17 | Kidney: 4/17 (24%)<br>Liver: 4/17 (24%)<br>Heart: 5/17 (29%)<br>Lung, heart+lung: 4/17 (24%) | 10/17 (59%) | First-line | R | 4 courses of rituximab monotherapy | 10/17: 59% (36-78) | 24 | 37·00 |
| Blaes et al* | Adults | 11 | Kidney: 4/11 (36%)<br>Heart: 1/11 (9%)<br>Lung: 5/11 (45%)<br>Pancreas+kidney: 1/11 (9%) | 6/7 (86%) | First-line and second-line | R, CHOP (1/11) | 4 courses of rituximab monotherapy, repeated every 6 months until progressive disease | 7/11: 64% (35-85) | 30 | 14·00 |
| Swinnen et al* | Adults | 16 | Kidney: 3/16 (19%)<br>Heart: 13/16 (81%) | 6/9 (67%) | First-line | None | R→followed by IFNα →followed by ProMACE CytaBOM, when complete response was not reached, patients progressed to the next step | R: 1/16; IFNα: 1/13; ProMACE CytaBOM: 5/7 | >60 | 19·00 |

Trappe R et al. Lancet Oncology 2012


Thank You!